FORM PTO-1390 (JC#69 98) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 21025-11
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S APPLICATION NO (If known, see 37 CFR 1 5) 09/787810
INTERNATIONAL APPLICATION NO. PCT/GB99/03172	INTERNATIONAL FILING DATE 22 September 1999	PRIORITY DATE CLAIMED 23 September 1998

TITLE OF INVENTION:

MICRONISED PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US

FLYNN, Richard Anthony, GOLDMAN, Martin Harris and LOVELY, James Richard

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U S C 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S. C. 371 (c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S C. 371(c)(3))
   a ☐ are transmitted herewith (required only if not transmitted by the International Bureau)
   b ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C F.R. 1 97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification
15. ☒ A change of power of attorney and/or address letter
16. ☒ Other items of information· Executed assignment document from Inventors to Applicant: **PHARMAX LIMITED**

U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/787810	INTERNATIONAL APPLICATION NO PCT/GB99/03172	ATTORNEY'S DOCKET NUMBER 21025-11

☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):	CALCULATIONS	PTO USE ONLY
Search Report has been prepared by the EPO or JPO.. ..... $		
International preliminary examination fee paid to USPTO (37 CFR 1.482) . .... $		
No international preliminary examination fee paid to USPTO (37 CFR 1 482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $860.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO . ... $		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provision of PCT Article 33(2)-(4) .. . . $		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**	
Surcharge of **$130** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	80 - 20 =	60	x **$18.00**	**$1080.00**	
Independent claims	4 - 3 =	1	x **$80.00**	**$80.00**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+$270.00**	**$270.00**	
	TOTAL OF ABOVE CALCULATIONS =			**$2,290.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.0, 1.27, 1.28).					
SUBTOTAL =					
Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					
TOTAL NATIONAL FEE =				**$2,290.00**	
Fee for recording the enclosed assignment (37 CFR 1 21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **$40** per property +					
TOTAL FEES ENCLOSED =				**$2,330.00**	
				Amount to be refunded	$
				Charged	$

a. ☒ Checks in the amount of $2290 00 and $40 00 to cover the above fees is enclosed

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayments to Deposit Account No. 16-2230. A duplicate copy of this sheet is enclosed

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted ton restore the application to pending status.

SEND ALL CORRESPONDENCE TO

OPPENHEIMER WOLFF & DONNELLY LLP
500 Newport Center Drive, Suite 700
Newport Beach, California 92660
Attn: Louis C. Cullman
Customer No: 25204

SIGNATURE:

Louis C. Cullman
NAME

39,645
REGISTRATION NUMBER

Patent Application
Attorney Docket: 21025-11

MICRONISED PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to PCT Application PCT/GB99/03172 filed September 22, 1999, published as WO00/16745 on March 30, 2000, which claims priority to Great Britain patent application GB 9820746.7, filed September 23, 1998.

BACKGROUND OF THE INVENTION

[0002] The present application relates to improvements in or relating to pharmaceutical compositions comprising micronised colistin sulphomethate sodium.

[0003] Colistin is an anti-bacterial cationic cyclic polypeptide belonging to the polymixin group. It is produced as a secondary metabolite of *Bacillus polymyxa* var. *colistinus*. Treatment of colistin base with formaldehyde and sodium bisulphite results in the production of colistin sulphomethate sodium. This is described in Japanese patent 4898/1957. The product is a crystalline powder which is soluble in water.

[0004] Colistin sulphomethate sodium is a combination of the negatively charged molecular ion colistin sulphomethate with positive sodium ions. It should be carefully distinguished from colistin sulphate. Both are described in the European Pharmacopoeia.

[0005] Colistin is of particular benefit in the treatment of serious infections caused by bacterial pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella sp.* An important property of colistin is that bacteria which are sensitive to the drug do not readily acquire resistance. Colistin as a pharmaceutical may be prepared into numerous different preparations, e.g. topical, bladder irrigation, oral such as tablets, or as intravenous or intra-muscular injections.

[0006] Colistin sulphate can be prepared from colistin. It is currently used to treat gram negative infections of the body such as intestinal infections due to various micro-organisms and, usually in association with other antibiotics, for the suppression of bowel flora. As noted above, colistin sulphate should be distinguished from colistin sulphomethate sodium.

[0007] Colistin sulphomethate sodium can also be prepared. It exists as a white to slightly yellow hygroscopic powder. It is commercially supplied at a particle size of 100-200 μm mass median diameter. The powder is highly soluble in water and as such is used for parenteral administration. As a powder, colistin sulphomethate sodium must be stored in air-tight containers, preferably protected from the light. Colistin sulphomethate sodium is used in the treatment of infections in patients suffering from cystic fibrosis, a genetic disease which affects many body systems, and which develops at a young age. Various glands of the body do not function properly. The disease is marked by a malfunction of the glands in the lining of the bronchial tubes. Instead of producing their normal thin mucus, the bronchial glands produce a thick, sticky mucus that stagnates in the tubes. Microbes are able to multiply readily, causing serious respiratory infections ultimately leading to respiratory failure. It is known that colistin sulphomethate sodium is effective in treatment of infections caused by these microbes e.g. *Pseudomonas aeruginosa*. The usual form of administration is as a solution for inhalation after nebulisation. The nebulised solution is prepared by taking a vial in which there is a known dosage of colistin sulphomethate sodium powder, injecting water into the vial and then inhaling the solution into the lungs through a nebuliser. Colistin sulphomethate sodium is poorly absorbed into the bloodstream. This is preferred as the bacteria can be attacked in the mucus which lines the lungs during illness.

[0008] Whilst jet nebulisation therapy has been shown to be successful, the nebulisation technique has several drawbacks. Jet nebulisers utilise compressed gases (usually air) to convert a drug solution into a spray. The compressed air passes through a narrow venturi orifice and negative pressure is created. Liquid is drawn from a fluid reservoir through a feed tube, fragments into droplets, and is accelerated to a velocity

sufficient for more than 99% of the droplet mass to impact on baffles or on the nebuliser where droplets coalesce and drain back into the fluid reservoir. Only 1% of the aerosol mass leaves the nebuliser directly. The outgoing air becomes saturated with water derived from liquid retained in the nebuliser, and this has two important consequences: Firstly, the nebuliser is cooled and reaches an equilibrium temperature approximately 10°C below ambient, so that the patient inhales a relatively cold spray. Secondly, the evaporation of water causes the concentration of solutes to increase with time.

[0009] There are many different designs of nebuliser available which use different flow rates of compressed gas. The output from these nebulisers will all be different and accordingly it is difficult for a patient to ensure that a constant dose is administered. The nebulisers themselves are bulky due to the compressors which are required. Although described as being transportable, the nebuliser/compressor system is not truly portable. When they are undergoing treatment, patients need to remain connected to the mouthpiece of the nebuliser for approximately 20 minutes in order to complete the therapy and in order to ensure that the correct dose is administered. An electrical supply is needed to run the nebuliser.

[0010] It will be seen from the above that, although colistin sulphomethate sodium is a valuable pharmaceutical in the treatment of infections occurring during cystic fibrosis and other bacterial infections, there are a number of disadvantages which mean that it is not widely accepted as a treatment regime, particularly for infants. It has been determined that many of the problems arise from the preferred delivery method described above, i.e. as a nebulised liquid.

[0011] WO 95/00128 (Astra) describes the delivery to the lungs of dry powder polypeptides. An enhancer compound is used to promote absorption into the systemic circulation. In contrast, colistin sulphomethate sodium is used very locally in the lungs - absorption into the bloodstream is not an objective.

[0012] US-A-5,767,068 (Pathogenesis) describes the separation and use of individual components of colistin sulphate. Colistin sulphate is separated into individual

components in free base form. Such components are described by Ebverdam, Larsen and Lund *(Journal of Chromatography, 218 (1981) 653-661)*.

[0013] WO-A-98/20836 is to be noted as the international publication which is equivalent to US-A-5,767,068.

[0014] *J. of Clinical Pharmacology and the J. of New drugs, 1970(10),274-281*, describes sodium colistimethate aerosols for use in the treatment of gram-negative infections of the respiratory tract. The aerosol is prepared by dissolving sodium colistimethate sterile powder in sterile water. When administered through a suitable nebuliser the aerosol has a particle size of 1-7 microns.

[0015] *Archives of Diseases in Childhood, 68,1993, 788-792*, describes the treatment of cystic fibrosis using aerosols. The paper refers to the delivery of micronised gentamicin powder using a Rotahaler (registered trade mark). It was found that the powder caused coughing. The paper concludes that aerosol forms of drugs delivered through a nebuliser are more suitable for treatment of cystic fibrosis.

BRIEF SUMMARY OF THE INVENTION

[0016] It has now been discovered that micronised colistin sulphomethate sodium can be administered to the airways of a patient using a powder dose inhalation device. The micronised colistin may be used alone or with a carrier, such as lactose.

[0017] According to the present invention, there is firstly provided the use of micronised colistin sulphomethate sodium in a method of treatment of the human body, particularly in the treatment of bacterial infections of the pulmonary system, most particularly in the treatment of secondary infections in patients suffering from cystic fibrosis, by powder inhalation.

[0018] According to a further aspect of the present application, there is provided a pharmaceutical composition comprising micronised colistin sulphomethate sodium and a carrier, in the absence of free liquid.

[0019] According to a yet further aspect of the present invention, there is provided a pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium, optionally together with a carrier, and a container. The container is preferably a capsule.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] Figure 1 shows a particle size analysis of micronised colistin sulphomethate sodium.

[0021] Figure 2 shows the structure of colistin sulphomethate with accompanying sodium ions.

[0022] Figure 3 shows a neutralised colistin base, as described in US-A-5,767,068.

DETAILED DESCRIPTION OF THE INVENTION

[0023] Micronised colistin sulphomethate sodium may be defined as being a powder wherein at least 90% by volume of the powder comprises particles have a diameter of less than 10 micrometers. Most preferably, at least 50% of the particles have a diameter of less than 8 micrometers. More preferably, at least 25% of the particles have a diameters of less than 6 micrometers.

[0024] Figure 1 shows a particle size analysis of micronised colistin sulphomethate sodium.

[0025] Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, a suitable particle

size range being 0.01-10, usually 1-8 micrometers. Particle sizes may be measured by a number of methods, e.g. by laser diffraction or microscope analysis.

[0026] Micronised colistin sulphomethate sodium may be prepared by fluid energy milling, ball milling, spray drying or precipitation. The colistin sulphomethate sodium may be administered in conjunction with a carrier. The carrier may be any non-toxic material which is chemically inert to the colistin sulphomethate sodium and will be acceptable for inhalation or for administration. Examples of carriers which may be used include inorganic salts, e.g. sodium chloride or calcium carbonate; organic salts, e.g. sodium tartrate or calcium lactate; organic compounds, e.g. urea; monosaccharides, e.g. lactose, arabinose or dextrose; disaccharides, e.g. maltose or sucrose; polysaccharides, e.g. starches and dextrans. A particularly preferred carrier is a lactose, e.g. crystalline lactose.

[0027] The present invention also provides a method for preparing a composition of the invention which comprises mixing together micronised colistin sulphomethate sodium and a carrier. The colistin sulphomethate sodium and the carrier may be blended in a drum, hoop or Y-cone blender as known in the art.

[0028] The carrier does not have to have the same particle size specification as the colistin sulphomethate sodium. The carrier may in fact generally be of a larger particle size than that of the colistin sulphomethate sodium in order to facilitate delivery from the inhalation device and yet not be deposited in the finer airways of the lungs. The inclusion of a carrier may ease dosage of pharmaceutical and carrier into capsules. Preferably at least 50%, and more desirably at least 70% by volume of the carrier particles have an effective particle size in the range of 30 to 150, especially 30 to 80, micrometers. The admixture of pharmaceutical and carrier may contain up to 75% by weight, more preferably up to 50% by weight of carrier. Generally the ratio of colistin sulphomethate sodium will be in the range of 5:1 to 1:2 preferably 4:1 to 1:1 by weight.

[0029] Colistin sulphomethate sodium is a negatively charged molecular ion with positively charged sodium counter ions. Figure 2 shows the structure. There are five

sulphomethate groups (CH_2-OSO_2^-). In contrast, Pathogenesis are producing a neutral base shown in Figure 3. US-A-5,767,068 refers to variable groups R_1 and R_2; R_1 is identified as 6-methyloctanoyl or 6-methylheptanoyl, and R_2 as sec-butyl, isobutyl or isopropyl.

[0030] It has now been surprisingly found that the negatively charged colistin sulphomethate ion (preferably in its sodium form) can be delivered to the lungs. As absorption into the blood stream is not wanted, the negatively charged ion is preferred to the base colistin.

[0031] It has been found that colistin sulphomethate sodium is a mixture of at least ten components. Tests carried out on mixtures of antibacterial preservatives show that the mixture of components found in colistin sulphomethate sodium show synergy of activity against gram negative microbial organisms.

[0032] It has been surprisingly found that water absorption of a micronised powder is comparatively low, e.g. approximately 5-7% by weight under normal atmospheric conditions. It has also been found that the micronised powder does not stick together. In powders having a larger particle size, the particles can stick together because of static forces. This sticking occurs will colistin and colistin sulphate. However, this is not found in the colistin sulphomethate sodium of the present invention. This is a further surprising advantage of the present application.

[0033] In addition to the micronised colistin sulphomethate sodium and, optionally, the carrier, the composition may contain other ingredients, such as colouring matter or flavouring agents such as saccharine, which may be present in inhalant compositions. Antistatic agents may also be added, e.g. as described in GB-A-2269992 (Rhone-Poulenc Rorer Ltd). It is preferred to use the minimum of such other ingredients.

[0034] The powder formulation may contain other pharmaceutical ingredients such as bronchodilators e.g. salbutamol Such other pharmaceutical ingredients preferably have an effective particle size similar to that of the colistin. The bronchodilatory drug

will be delivered in very small (microgram) quantities. For example a capsule may contain from 50 to 150, e.g. 125, milligrams of colistin sulphomethate sodium and from 1 to 250, e.g. 200, micrograms of salbutamol.

[0035] The micronised powder may be delivered to the lungs through a specialised powder inhalation device. Most preferred is location of the powdered pharmaceutical within a hard capsule or a blister package. The capsule or blister is ruptured or broached within the inhaler device, thereby enabling the powder to be inhaled through the mouthpiece as air is sucked in.

[0036] There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a capsule containing colistin sulphomethate sodium, preferably in the form of a pharmaceutical composition of the present invention. The capsule may be formed of gelatin or a plastics material.

[0037] By carefully controlling the conditions under which capsules and blisters and filled, the final moisture level in the product can be kept to below 15 wt %, preferably below 5 wt %. The humidity level is preferably below 25% RH, most preferably below 15% RH. The low moisture level is important for product stability, and enables the product to be filled with minimal static effects. Flow out of the capsule or blister is also improved.

[0038] By careful selection of capsule and packaging components, stability and dosing can be controlled. The level of lubricant is kept low (preferably below 0.2% wt %). Capsules for oral use usually contain 2-3 wt % lubricant. Mould lubricant could interact with the dry powder. Capsule integrity is important, and accordingly a peelable lid to the blister package is preferred to a conventional "push out" seal. The blister may be, e.g. aluminium (40-50 μm thick) laminated with PVC (50-70 μm thick) and PA (20-30 μm thick). The peelable seal may be formed of soft aluminium (18-22 μm thick) laminated with PE7 (20-25 μm thick).

[0039] The amount of composition contained in the capsule will, of course, depend upon the desired dosage. However, the capsule suitably contains from 10 to 200 milligrams, most preferably 30 to 150 milligrams of the colistin sulphomethate sodium. The colistin sulphomethate sodium may be delivered with or without a carrier. If a carrier is used then clearly a larger amount of the mix of carrier and pharmaceutical is required. It has been found that the capsule should contain a larger dose of drug than the amount which will actually be delivered to the lungs. Dosages are usually expressed in "units". 80 mg of colistin sulphomethate is equivalent to approximately 1 million units of colistin sulphomethate. One unit of colistin sulphomethate is contained in 0.00007874 mg of the first International Reference Preparation (1966) of colistin sulphomethate. Children with cystic fibrosis may be treated with nebulised colistin sulphomethate sodium at a level of 500,000 units, twice daily. The respirable fraction from a conventional nebuliser (CR 50 System 22) is approximately 9 mg of colistin sulphomethate sodium from a 500,000 unit dose. This can be tested using a multistage impinger and measuring mass collected at stages 3 and 4.

[0040] A preferred device for delivering the pharmaceutical composition according to the present invention is the Turbospin (Registered Trade Mark) originating from PH & T. This device uses a gelatin capsule which is pierced in the bottom by a single metal needle. When the patient inhales through the mouthpiece, air is drawn in through the tangentially ranged slits around the chamber. This spins the capsule and throws out the contents into the airstream. A flip top on the device allows up to three spare capsules to be stored. Another preferred device for delivering the pharmaceutical composition is the Aerohaler (Registered Trade Mark) from Boehringer Ingelheim. This device uses a hard gelatin capsule which is pierced by two metal needles in the side of a capsule. When the patient inhales through the mouthpiece, air enters the bottom of the chamber causing the capsule to spin and throw out its contents into the airstream. The unit holds six capsules in a carousel cartridge. When all six capsules have been used, the unit locks and it must be re-loaded. Other devices known in the art for delivery of encapsulated powders by inhalation can be used.

[0041] The capsule keeps the powder dry and thus in flowable form. The capsules should preferably be designed to protect their contents from light, e.g. they should be opaque or the capsules may be packed and/or stored in opaque containers, e.g. coloured or covered containers, or metal foil.

EXAMPLES

Example 1

[0042] Micronised colistin sulphomethate sodium was produced by fluidised energy milling using a Hosokawa Alpine mill of powdered colistin sulphomethate sodium having an average particle size of approximately 100 μm supplied by Dumex Pharmaceuticals. A sample of the micronised colistin sulphomethate sodium was suspended in chloroform and the particle size analysed by a laser counter. Figure 1 shows the range of particle sizes of the micronised colistin.

Example 2

[0001] Gelatin pharmaceutical capsules (standard size 2) were obtained from Shionogi Qualicaps. The capsules were filled using a standard dosator (Zanassi LZ64) under controlled temperature and humidity conditions (17°C/10%-15% RH). Colistin sulphomethate sodium was filled into the capsules either as pure micronised powder or together with a lactose carrier (lactose monohydrate lactochem pharmaceutical grade from Borculo Whey Products). The fills are as shown on Table 1.

Table 1

Run Number	Mix Used	Total Fill
1	Colistin	125 mg
2	Colistin/Lactose (1:1)	165 mg
3	Colistin/Lactose (2:1)	140 mg
4	Colistin/Lactose (4:1)	130 mg
5	Colistin	125 mg

[0002] When colistin sulphomethate sodium is used alone, it flows well. Filling weights are standard. If a mixture of colistin to lactose as in Run 2 is used then the mixed powder flows well through the machine but there is sticking of the components of the dosator. Sticking reduces in Runs 3 and 4. Tests found respirable fractions in the region of 16 to 20 mg. This is the mass of colistin sulphomethate sodium collected on stages 3 and 4 of the multistage liquid impinger and equates to particles having a size less than about 3 to 4 micrometers.

Example 3

[0003] Filled capsules produced from Runs 1 to 4 above were stored for nine months under various humidity conditions. There was no degradation or clumping of the colistin sulphomethate sodium. There was no noticeable clumping of colistin sulphomethate sodium on the capsule walls.

Tests

[0004] Clinical trials were carried out. In one trial, the absorption of the powdered colistin sulphomethate sodium into the airways of the lungs was measured (specific airway conductance). It was found that 80% of patients, inhaling the micronised dry powder colistin sulphomethate sodium, were able to mobilise 80 mg of the drug, i.e. 1 mega unit. This is a very high uptake, and more than would be expected from a

powdered drug. The powder does not cause irritation, and thus construction, of the lungs.

[0005] In a second trial, patients were given a premedication dose of 200 micrograms of salbutamol. This appeared to improve airway conductance.

[0006] In an alternative medication regime, the salbutamol can be mixed into the same capsule as the colistin sulphomethate sodium.

[0007] A further trial compared specific airway conductance, as measured by whole body plethysmography, of traditional nebulised colistin sulphomethate sodium and dry powder. There did not seem to be any noticeable difference.

[0008] The foregoing description addresses embodiments encompassing the principles of the present invention. The embodiments may be changed, modified and/or implemented using various types of arrangements. Those skilled in the art will readily recognize various modifications and changes which may be made to the invention without strictly following the exemplary embodiments and applications illustrated and described herein, and without departing from the scope of the invention which is set forth in the following claims.

What is claimed is:

1. Micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers for use in the treatment of a pulmonary infection by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

2. Colistin sulphomethate sodium for the use as claimed in Claim 1 wherein the micronised powder is mixed with a carrier.

3. Colistin sulphomethate sodium for the use as claimed in Claim 2 wherein the carrier is lactose.

4. A composition comprising micronised colistin sulphomethate sodium as defined in Claim 1 and a carrier, in the absence of free liquid.

5. A composition as claimed in Claim 4 wherein the carrier is lactose.

6. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 5:1 to 1:2 by weight.

7. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 4:1 to 1:1 by weight.

8. The composition as claimed in any one of Claims 4 to 7 wherein at least 50% by volume of the carrier particles have an effective particle size in the range of 30-150 micrometers.

9. A composition as claimed in any one of Claims 4 to 8 wherein at least 50% by volume of the micronised colistin sulphomethate sodium has a particle diameter of less than 8 micrometers.

10. A composition as claimed in any one of Claims 4 to 9 wherein at least 25% of the particles of micronised colistin sulphomethate sodium have a diameter of less than 6 micrometers.

11. A composition as claimed in any one of Claims 4 to 10 wherein the micronised colistin sulphomethate sodium is prepared in the desired particle size range using a fluid energy mill.

12. A process for the preparation of a composition as claimed in any one of Claims 4 to 11 which comprises mixing micronised colistin sulphomethate sodium and a carrier.

13. A pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium wherein at least 90% by volume of the particles have a diameter less than 10 micrometers or a composition according to any one of Claims 4 to 11 and a container, said dosage having a content of below 10 wt % water.

14. A pharmaceutical dosage form according to Claim 13 wherein the container is a hard gelatin capsule.

15. A capsule containing micronised colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers.

16. A capsule as claimed in Claim 15 containing from 10 to 200 milligrams of micronised colistin sulphomethate sodium.

17. A capsule as claimed in Claim 15 containing from 30 to 150 milligrams of micronised colistin sulphomethate sodium.

18. A capsule as claimed in any one of Claims 15 to 17 further comprising a carrier.

19. A capsule as claimed in Claim 18 when the carrier is lactose.

20. A capsule according to any one of Claims 15 to 19 which is opaque.

21. A capsule according to any one of Claims 15 to 19 or a composition according to any one of Claims 4 to 11 packed in an opaque container.

22. A capsule containing micronised colistin sulphomethate sodium when the micronised particles have a diameter of less than 10 micrometers, in unit dosage form.

23. A capsule according to any one of Claims 15 to 22 which additionally comprises a micronised bronchodilatory drug.

24. A capsule according to Claim 23 wherein the bronchodilatory drug is salbutamol.

25. A capsule according to Claim 23 or Claim 24 which comprises from 50 to 150 milligrams of colistin sulphomethate sodium and from 1 to 250 micrograms of bronchodilatory drug

26. Micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers for use in the treatment of a pulmonary infection by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

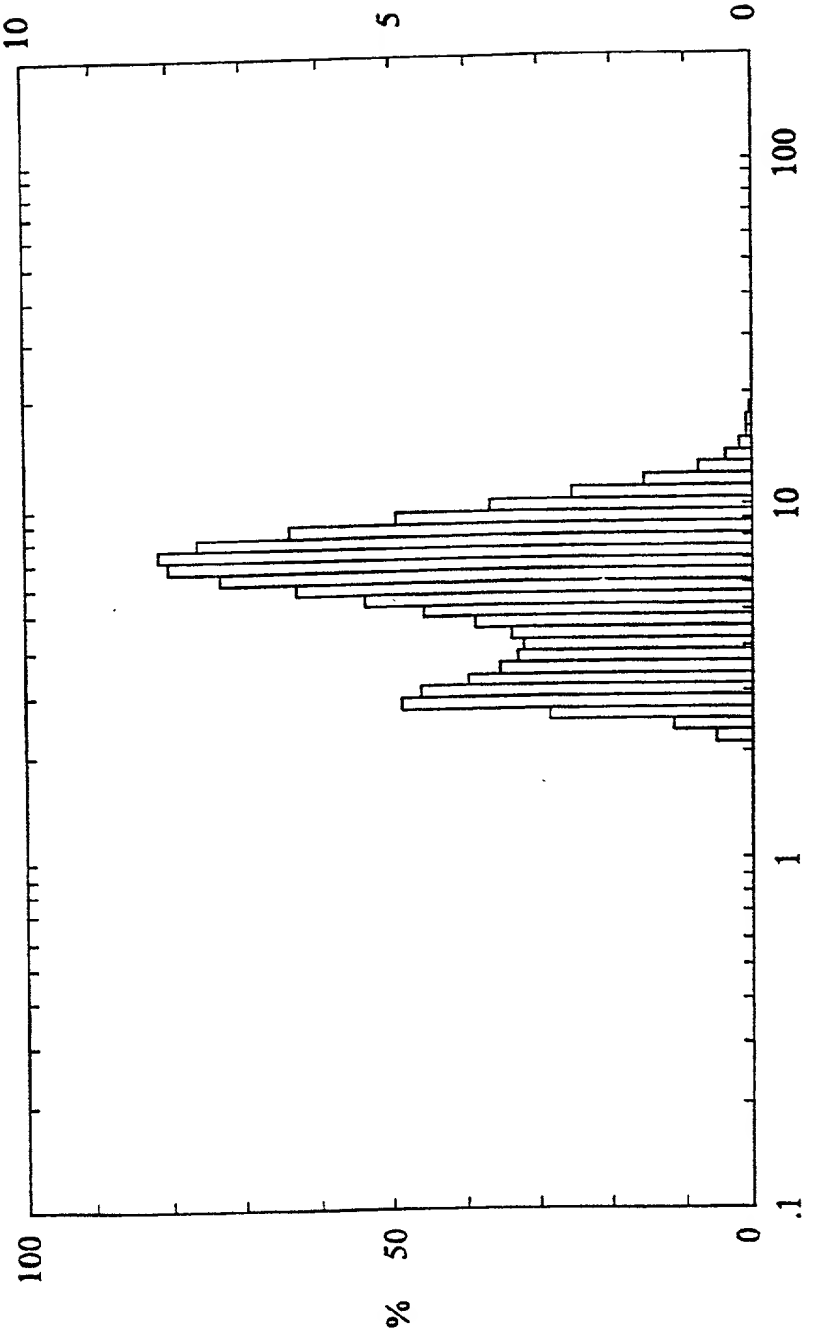
27. Colistin sulphomethate sodium for the use as claimed in Claim 26 wherein the micronised powder is mixed with a carrier.

28. Colistin sulphomethate sodium for the use as claimed in Claim 27 wherein the carrier is lactose.

MICRONISED PHARMACEUTICAL COMPOSITIONS

ABSTRACT

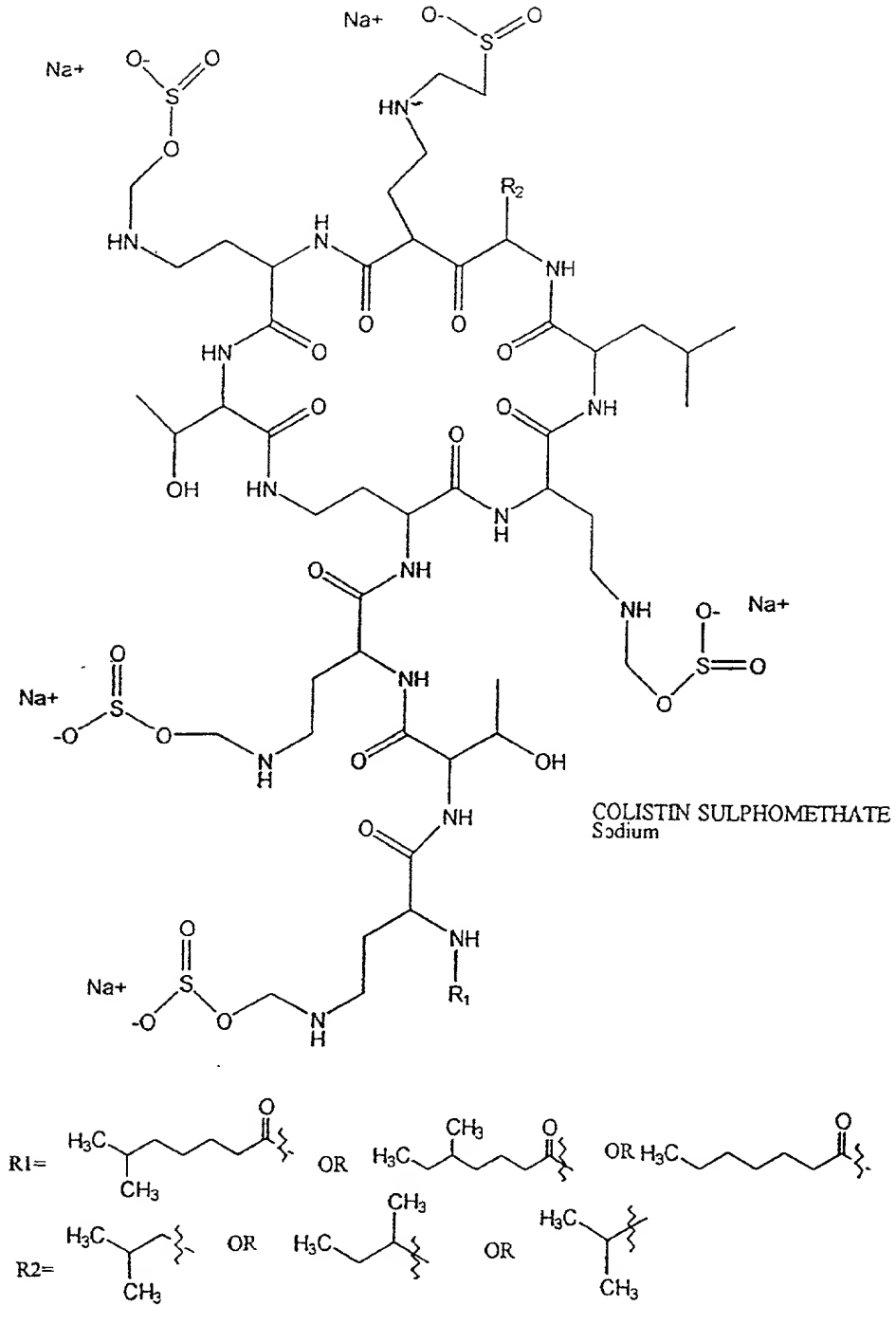
Pharmaceutical compositions are described comprising micronised colistin sulphomethate sodium. The micronised pharmaceutical may be used together with a carrier such as lactose. The pharmaceutical compositions may be packed into containers such as gelatin capsules and administered by powder inhalation.



Particle sizing of micronised colistin sulphomethate sodium

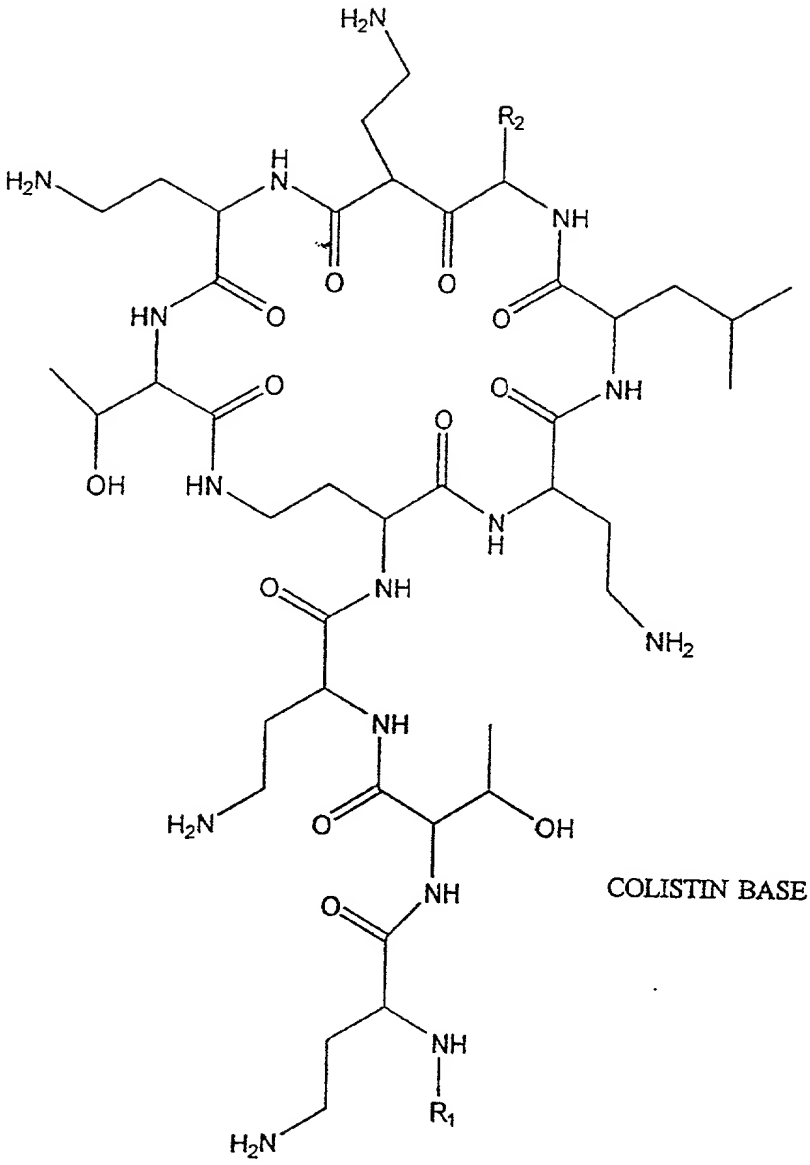
FIG. 1

FIG. 2

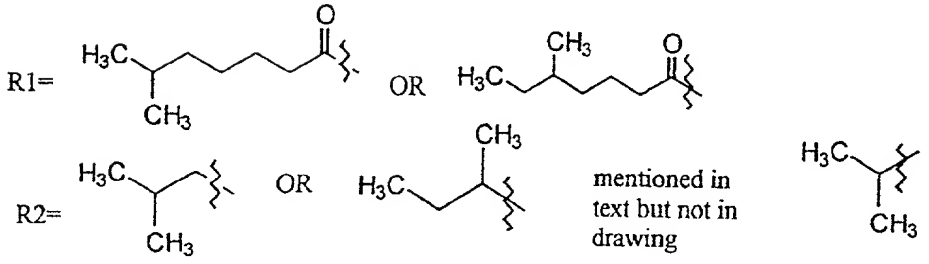


COLISTIN SULPHOMETHATE
Sodium

FIG. 3



COLISTIN BASE



PATENT
Docket No. UDL-11

COMBINED DECLARATION AND PETITION

As a below named inventor, I hereby declare that:

This declaration is of the following type:

- ☐ original
- ☐ design
- ☐ supplemental
- ☒ national stage of PCT
- ☐ divisional
- ☐ continuation
- ☐ continuation-in-part

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled MICRONISED PHARMACEUTICAL COMPOSITIONS, the specification of which:

(a) ☒ is attached hereto
(b) ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).
(c) ☐ was described and claimed in PCT International Application No. _____, filed on _____ and as amended under PCT Article 19 on _____ (*if any*).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application of which priority is claimed.

(d) ☐ no such applications have been filed
(e) ☒ such application have been filed as follows:

Country (or indicate if PCT)	Application Number	Date of Filing (day, month, year)	Priority Claims Under 37 USC 119
GB	9820746.7	9/23/98	☒ Yes ☐ No
PCT	GB99/03172	9/22/99	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a), regarding events which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status-patented, pending, abandoned

PATENT
Docket No. UDL-11

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Wherefore I pray that Letters Patent be granted to me for the invention or discovery described and claimed in the foregoing specification and claims, and I hereby subscribe my name to the foregoing specification and claims, declaration, power of attorney, and this petition.

Full Name of Sole or First Inventor: Richard Anthony FLYNN	
Inventors Signature: K Flynn	Date Signed: 12 March 2001
Residence (City, State and/or Country): Kent, United Kingdom GBX	Citizenship: GB
Post Office Address(Street, City, State, Zip Code, Country): 69 Chestnut Grove, Wilmington, Kent DA2 7PQ, UK	

Full Name of Second Inventor: Martin Harris GOLDMAN	
Inventors Signature: K Goldman	Date Signed: 12 March 2001
Residence (City, State and/or Country): London, United Kingdom GBX	Citizenship: GB
Post Office Address(Street, City, State, Zip Code, Country): 19 Myddleton Park, London N20 0HT, UK	

Full Name of Third Inventor: James Richard LOVELY	
Inventors Signature: James Lovely	Date Signed: 12/March 2001
Residence (City, State and/or Country): London, United Kingdom GBX	Citizenship: GB
Post Office Address(Street, City, State, Zip Code, Country): 65 Longridge Road, London SW5 9SG, UK	

CERTIFICATE OF MAILING

I hereby certify that on _____, this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231.

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Angela Wendel

Name of Person Signing: ANGELA WENDEL

PATENT

Applicant: **Flynn et al.**
Serial No.: **Unknown**
Filed:
Title: **MICRONISED PHARMACEUTICAL COMPOSITIONS**
Examiner: **Unassigned**
Group Art Unit: **Unassigned**
Atty Docket No.: **UDL-11**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY BY ASSIGNEE AND EXCLUSION OF INVENTOR UNDER 37 C.F.R. § 1.32

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Pharmax Limited, having become the owner of all rights in and to the above-identified application by virtue of an Assignment executed by the inventors, said Assignment being submitted concurrently herewith for recording, hereby appoint the following as the attorneys of record with full power of substitution and revocation, to transact all business in the Patent and Trademark Office and before competent International Authorities connected with above-referenced patent or patent application; said appointment to be to the exclusion of the inventors and their attorneys in accordance with the provisions of 37 C.F.R. § 1.12:

C. BERMAN, REG. 29249
L. J. BOVASSO, REG. 24,075
M. E. BROWN, REG. 28,590
B. CANTER, REG. 34,792
D.G. CHAPIK, REG. NO. 43,424
L. C. CULLMAN, REG. 39,645
C. DARROW, REG. 30,166
W.G. EDWARDS, REG. NO. 44,426
M. FARBER, REG. 32,612
C. A. S. HAMRICK, REG. 22,586
S. R. HANSEN, REG. 38,486
M. D. HARRIS. REG. 26,690
M. HEYNINCK, REG. 44,763
J. W. INSKEEP, REG. 33,910
H. D. JASTRAM, REG. 19,777
A. KAMRATH, REG. NO. 28,227
D. N. LARSON, REG. 29,401
J. LAZARIS, REG. 45,981
C.J. LERVICK. REG. NO. 35,244
K. A. MACLEAN, REG. 31,118
D. MCKINLEY, REG. NO. 42,867
C.A. MORTON, REG. NO. 44,954
S. OH, REG. P45,583
W. POMS, REG. 18,782
A. C. ROSE, REG. 17,047
C. ROSENBERG, REG. 31,464
G. P. SMITH, REG. 20,142
R.S. TAMURA, REG. 43,179
G.B. WOOD, REG. 28,133

whose address is:

OPPENHEIMER WOLFF & DONNELLY LLP
Attn: Louis C. Cullman, Esq.
500 Newport Center Drive, Suite 700
Newport Beach, CA 92660
Telephone: (949) 823-6000
Facsimile: (949) 823-6040

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned, whose title is supplied below, is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Pharmax Limited

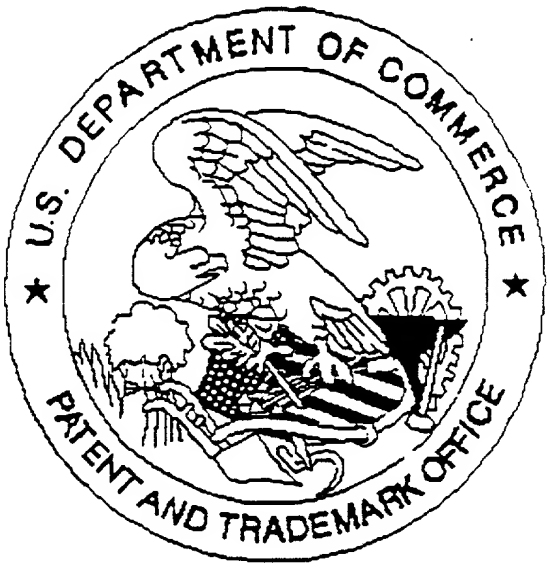
Dated: 14 MARCH 2001

A. Livingstone

Name: ANDREW LIVINGSTONE
Title: COMPANY SECRETARY

United States Patent & Trademark Office

Office of Initial Patent Examination -- Scanning Division



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